

REMARKS**Species Election**

The Examiner contends that the search for all diseases and all augmenting agents places an undue burden on the PTO because "the search of one disease does not encompass the search for a second disease/disorder and the search for all diseases". Applicants respectfully disagree with this assessment.

Applicants submit that it would not place an undue burden upon the Examiner to search a *class* (genus) of augmenting agents and disorders. A search of the prior art for one member of a *class* of augmenting agents and one member of a *class* of disorders would also identify prior art that is applicable to the other members. Accordingly, reconsideration of the requirement is respectfully requested.

Rejection of Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Takayama *et al.* (U.S. Pat. No. 5,817,670), Katzung (*Basic & Clinical Pharmacology*, page 195 (1995)) and Tully *et al.* (WO96/11270) in view of Calvanio *et al.* (*Neurol. Clin.*, 11(1):25-57 (1993)).

*Teachings of the Cited References***Takayama *et al.***

Takayama *et al.* is cited by the Examiner as teaching that "phosphodiesterase inhibitors, known to result in accumulation of cAMP, are known to be useful in a method of treating stroke". Paper No. 9, at page 3, lines 11-13. Takayama *et al.* teach the use of phosphodiesterase inhibitors in the treatment of stroke (column 6, line 4) but do not teach or suggest the use of phosphodiesterase inhibitors in the treatment of cognitive deficits associated with stroke. In addition, as acknowledged by the Examiner, Takayama *et al.* do not teach or suggest combining any phosphodiesterase inhibitor treatment with a cognitive training protocol.

Katzung

Katzung is cited by the Examiner as also teaching at page 195 that "phosphodiesterase inhibitors, known to result in accumulation of cAMP, are known to be useful in a method of treating stroke". Paper No. 9, at page 3, lines 11-13. This characterization of the teachings at page 195 is incorrect. In fact, it is stated at page 195 that "Drugs that inhibit phosphodiesterases, the family of enzymes that inactivate cAMP and cGMP, have long been used in therapy of *heart failure*" (emphasis added). Heart failure is distinct from stroke. Heart failure occurs when the heart is unable to pump blood effectively throughout the body. As a result, some of the blood that is normally pumped out of the heart backs up into the lungs and other parts of the body. In contrast, stroke is a sudden decrease or interruption in blood flow to the brain caused by: (1) the total obstruction of any artery that delivers blood to the brain; (2) rupture of a blood vessel in the brain, followed by hemorrhaging into the brain tissue; or (3) atherosclerosis. As such, this reference adds little, if anything, to the teachings of Takayama *et al.*

Tully *et al.*

Tully *et al.* is cited by the Examiner as teaching "a method of regulating long term memory in an animal comprising inducing of expression of a dCREB2 gene encoding a cAMP responsive activator". Paper No. 9, at page 3, lines 14-16. Tully *et al.* teach methods of modulating long term memory based on differential regulation of CREB activators and CREB repressors but do not teach or suggest the specific use of phosphodiesterase inhibitors in the treatment of cognitive deficits associated with stroke. In addition, as acknowledged by the Examiner, Tully *et al.* do not teach or suggest combining any drug treatment with a cognitive training protocol for use in treating cognitive deficits associated with stroke.

Calvanio *et al.*

Calvanio *et al.* is cited by the Examiner as teaching "the benefits of training to stroke patients", specifically that "learning can be accelerated and produce a higher level of outcome" "by detecting and controlling attentional functioning in specific tasks". Paper No. 9, at page 3, lines 18- 20. Calvanio *et al.* discuss various training procedures to alleviate cognitive deficits in

stroke survivors but do not teach or suggest combining training with any drug treatment, such as phosphodiesterase inhibitor treatment.

The Combination of References

In support of the rejection, the Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art "to treat stroke patients employing a combination of phosphodiesterase inhibitors and training". Paper No. 9, at page 4, lines 1-3. The Examiner alleges that one of ordinary skill in the art would be motivated to do so because "both PDE inhibitors and cognitive training are known to be useful in method of treating stroke". Paper No. 9, at page 4, lines 4-6. The Examiner contends that "one of ordinary skill in the art would have reasonably expected a combination of training and PDE inhibitors to be useful in treating stroke patients." Paper No. 9, at page 4, lines 6-8.

Applicants respectfully submit that this rejection is improper because the Examiner has not identified a suggestion in the prior art of the desirability of the proposed combination of references. Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). The only document of record which suggests the desirability of the proposed combination is Applicants' specification. However, the use of the present specification as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Notwithstanding the above, a *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not Applicants' disclosure. Id.

The Court of Appeals for the Federal Circuit has stated that "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole*." See, e.g., Kimberley-Clark Corp. v. Johnson & Johnson Co., 223 U.S.P.Q. 603, 609 (Fed. Cir. 1984). See also Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir.

1984). It is not proper to pick and choose among individual elements of assorted prior art references to recreate the claimed invention. Smithkline Diagnostics Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (Fed. Cir. 1988); Akzo N.V. v. International Trade Comm., 11 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986).

None of the cited references (Takayama *et al.*, Katzung, Tully *et al.*, Calvanio *et al.*), alone or in combination, would have suggested the claimed invention to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, would have suggested to one of ordinary skill in the art at the time the invention was made, with a reasonable expectation of success, treatment of a cognitive deficit associated with stroke by using Applicants' augmented cognitive training method. None of the cited references, alone or in combination, would have suggested to one of ordinary skill in the art at the time the invention was made, with a reasonable expectation of success, Applicants' augmented cognitive training method which comprises a specific cognitive training protocol and administration of an augmenting agent which enhances CREB pathway function, such as a phosphodiesterase inhibitor. As discussed above, Takayama *et al.* teach the use of phosphodiesterase inhibitors in the treatment of stroke, but do not teach or suggest the use of phosphodiesterase inhibitors in the treatment of cognitive deficits associated with stroke or the combining of phosphodiesterase inhibitor treatment with cognitive training methods. Katzung teaches the use of phosphodiesterase inhibitors in therapy of heart failure, which is distinct from stroke. Tully *et al.* teach methods of modulating long term memory based on differential regulation of CREB activators and CREB repressors, but do not teach or suggest the use of phosphodiesterase inhibitors in the treatment of cognitive deficits associated with stroke or the combining of drug treatment with cognitive training methods. Calvanio *et al.* teach several cognitive training methods for use in stroke rehabilitation, but do not teach or suggest the combining of training methods with drug treatment, such as phosphodiesterase inhibitor treatment. Accordingly, the cited references, either alone or in combination, would not have suggested the claimed invention to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

Reconsideration and withdrawal of the rejection Claims 1, 3-8, 11, 14-20, 23, 49-58, 60-64 and 94-106 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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